REMARKS

Claims 1-2 and 4-20 were pending. Upon entry of this amendment claims 1-2 and 4-42 will be pending.

Claim 1 has been amended. Support for the amendment to claim 1 can be found throughout the application as filed, especially at pages 6-8 of the application.

New claims 21-42 have been added and find support throughout the application as originally filed including, *inter alia*, at Tables 1 and 2. For example, Table 1 (pages 83-84), lists numerous compounds that inhibit human caspase 7 expression "by at least 60%".

No new matter has been added.

Rejections under 35 U.S.C. § 112

Claim 11 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully request reconsideration because Applicants provide sufficient written description of the claimed invention.

The Office alleges that the specification as filed:

> contains only a general definition of the term 'active sites'; it does not provide a description of the actual active sites that might be targeted by the invention of the instant application. Additionally, the specification only provides that such sites are experimentally determined; no further identification of sequences encoding any active sties has been described that might lead one of skill in the art to recognize that applicants were in possession of the claimed entities at the time of filing."

(Office Action, page 2). The Office further alleges that since "applicant has not described such characteristics, the skilled artisan would not have been able to envision what constitutes the specific active sites as claimed in the instant application." (Office Action, pages 2-3). Because the application as filed provides numerous examples of active sites, Applicants respectfully disagree.

Possession of an invention can be shown in a variety of ways. For example, the M.P.E.P. states:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

(M.P.E.P. § 2163, citations omitted). Applicants submit that, by the standard imposed in the M.P.E.P., Applicants have amply described "active sites." For example, according to the present specification:

> Antisense and other compounds of the invention which hybridize to the target and inhibit expression of the target are identified through experimentation, and the sequences of these compounds are ***hereinbelow identified*** as preferred embodiments of the invention. ***The target sites to which these sequences are complementary are hereinbelow referred to as "active sites"*** are therefore preferred sites for targeting.

(Specification, page 9, lines 30-37, emphasis added). Tables 1 and 2 include data obtained using compounds that inhibit the expression of human and mouse caspase 7. The compounds in the Table 1 are "compound[s] 8 to 50 nucleobases in length which specifically hybridize with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding caspase 7 (SEQ ID NO:3)." (Claim 11). Each compound is complementary to a target site and, as described above, the specification states, "[t]he target sites to which these sequences are complementary are...referred to as 'active sites." The skilled artisan would readily acknowledge that Applicants were in possession of the claimed invention at the time the application was filed.

Applicants have also described the distinguishing identifying characteristics sufficient to show that Applicants were in possession of the claimed invention (see, Table

1). Accordingly, Applicants respectfully request that the rejection of claim 11 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 15-20 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an enabling disclosure. The Office Action asserts that "the specification while being enabling for antisense-mediated inhibition of caspase 7 expression *in vitro*, does not reasonably provide enablement for *in vivo* antisense-mediated inhibition of caspase 7 *in vivo*." (Office Action, page 3). The Office alleges that the use of antisense compounds *in vivo* is "highly unpredictable" and is not enabled by the present application. (Office Action, page 4). The Office also alleges that "a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic." (Office Action, page 4). Applicants respectfully disagree and assert that the claimed invention is amply enabled.

The present application teaches the skilled artisan how to make and use the claimed invention. The crux of the rejection set forth by the Office appears to be that the present application, and also the prior art, allegedly does not support a correlation of *in vitro* results with *in vivo* results, especially when there are no working *in vivo* examples in the present application. In support of its allegations that the field of antisense is unpredictable, the Office cites Braasch and Corey, *Biochemistry*, **2002, 41**:4503-4510 (hereinafter the "Braasch reference"), Agrawal, *TIBTECH*, **1996**, **14**:376-387 (hereinafter, the "Agrawal reference"), Branch, *TIBS*, **1998**, **23**:45-50 (hereinafter, the "Branch reference"), Tamm *et al.*, *The Lancet*, **2001**, **358**:489-497 (hereinafter, the "Tamm reference"), and Gewirtz *et al.*, *PNAS*, **1996**, **93**:3161-3163 (hereinafter, the "Gewirtz reference") in the most recent Action dated February 7, 2003. None of the cited references, however, support the Office's position.

Applicants respectfully assert that the Office has mischaracterized the cited references. The Office cites the Braasch reference as stating, "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable." (Office Action, page 4). However, the Office has failed to put this statement in context of the rest of the article. The cited

sentence refers to the "practice over the past decade" (the Braasch reference, page 4503), not the state of antisense art at the time the application was filed. In fact, Braasch states that they will "summarize the substantial recent progress in the application of antisense and antigene oligomers for functional genomics and drug development." (See, page 4504 of the Braasch reference). The authors of the Braasch reference further state, "Recently, two trials have generated favorable preliminary findings that have substantially increased optimism about antisense as a general therapeutic approach...Since the pharmacokinetic properties of oligonucleotides are likely to be similar regardless of oligonucleotide sequence, progress in the Genasense and ISIS 3521 trials encourages the belief that it will be possible to target many other genes successfully." (*Id.*, p. 4506). Additionally, the Braasch reference states, "The use of oligonucleotides to control gene expression has long fascinated researchers because of the potential to rapidly generate potent and specific agents. In the ***past***, antisense technology has not always kept pace with expectations, but ***recent advances*** in diverse areas are likely ***to make it a routine and trusted research tool***." (*Id.*, p. 4509; emphasis added). The Braasch reference further states that "experience in the clinic is demonstrating that even older generation oligonucleotide designs are effective drugs, and a detailed database of pharmacological information is being developed." (*Id.*, p. 4504).

With respect to statements in the Office Action questioning an oligonucleotide's ability to reach its target, Braasch states:

> In contrast to the situation in cell culture, uncomplexed oligonucleotides that contain phosphorothioate linkages spontaneously enter some tissues when introduced intravenously. Delivery to the liver and kidney is most efficient, but the spleen, intestine, and other organs also receive significant doses. Promising data from ongoing clinical studies also suggest that oligomers can enter human tumors upon intravenous administration and produce a therapeutic effect. Oligonucleotides exhibit some oral bioavaailability, and this may prove a useful route for clinical administration in the future."

(*Id.*, p. 4504). Therefore, when taken in its entirety, the Braasch reference does ***not*** indicate that state of the art in antisense technology is highly unpredictable and unproven, as the Office alleges. In fact, the Braasch reference teaches quite the opposite, describing

"substantial recent progress" in antisense technology and "recent advances . . . likely to make it a routine and trusted research tool."

The Tamm reference also does not support the Office's conclusion that the field of antisense is unpredicatable. In fact, the Tamm reference discusses the ***successful*** clinical studies of several antisense oligonucleotides and paints an optimistic picture of the future of antisense technology. For example, the Tamm reference states that "[T]he specificity of this mechanism [antisense] has resulted in a new class of drugs with a wide range of potential clinical applications. One approved drug, and results of several clinical antisense drug trials, show the feasibility of this approach, with some evidence for clinical efficacy." (See, page 489 of the Tamm reference). The Tamm reference further describes the results of a systemic administration of antisense oligonucleotidues resulting in the downregualtion of the target protein within the target tissue, stating that "[t]his study is a milestone in the field of antisense, since the results suggest that the principle of antisense works, not only with local treatment, as shown with fomivirsen, but also with systemic treatment with antisense oligonucleotides." (*Id.*, p. 495).

The Office alleges that the Gewirtz reference teaches that the "inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target." (Office Action, page 5). However, the Gewirtz reference does not teach that antisense technology does not work, rather it focuses on how some oligonucleotides are less efficient than others and what factors may play a role in this. The authors discuss differences in structure and other chemical properties. The Gewirtz reference concludes by stating, "Nevertheless the potential power of [antisense] remains undisputed." (See, page 3162 of the Gewirtz reference).

According to the Office, the Branch reference states, "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." (Office Action, page 5). The Branch reference, however, does ***not*** teach that such barriers are insurmountable. Rather, the Branch reference concludes by stating, "there is growing evidence that antisense molecules can be useful pharmacological tools when applied carefully," (See, page 50 of the Branch reference), indicating that the skilled artisan sees

promise in the use of antisense. Branch does ***not*** state, however, that any such experimentation would be undue.

The M.P.E.P discusses the issue of correlation of *in vitro* and *in vivo* data. The M.P.E.P is very clear that it is the overall state of the art that is important for determining the unpredictability of a field, not one or two references. Indeed, the M.P.E.P states:

> In this regard, the issue of 'correlation' is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, ***the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.*** In *re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications)...***A rigorous or an invariable exact correlation is not required*** as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224, USPQ 739, 747 (Fed. Cir. 1985).

(M.P.E.P 2164.02, emphasis added).

It appears that the Office is under the impression that an "exact correlation" is required, while the M.P.E.P clearly states that it is not. Enablement does not require 100% success. In *Wands*, the claims were found to be enabling even though only 4 out of 143 (only 2.8%) hybridomas producing monoclonal antibodies were successful. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988).

In addition, the Office has failed to take into account numerous references which more accurately describe the status of the field of antisense technology at or prior to the filing date of the present application (November 8, 2001). Indeed, the state of the prior art as a whole does not support the Office's position. A recent survey of the relevant scientific literature demonstrates that there is a correlation between *in vitro* results and *in vivo* data in the field of the present invention and that *in vivo* use is not unpredictable. This survey demonstrates numerous examples of correlation between *in vitro* experiments and *in vivo* experiments. For example, in Smith *et al.* (*Clinical Cancer Research*, **7**:400-406, February 2001), data is discussed demonstrating inhibition of bcl-2 expression *in vitro* and *in vivo*. In Dwyer *et al.* (*Clinical Cancer Research*, **5**: 3977-3982, December

1999), the administration of an antisense compound inhibited the expression of *c-raf*-1 mRNA *in vitro* and *in vivo*. Based on these results the authors performed a clinical trial in human patients where expression of *c-raf-1* was inhibited. In Miyake *et al.*, (*Clinical Cancer Research*, **6**:1655-1663, May 2000) the authors provide data that demonstrate the inhibition of TRPM-2, both *in vitro* and *in vivo*. In Wang *et al.*, (*Clinical Cancer Research*, **7**:3613-3624, November 2001) the authors discuss *in vitro* inhibition of *mdm-2* expression followed by data demonstrating *in vivo* inhibition of *mdm-2* expression. In Berg *et al.*, (*The Journal of Pharmacology and Experimental Therapeutics*, **298**:477-484, 2001) the authors demonstrate *in vitro* and *in vivo* inhibition of thymidylate synthase expression. Tortora *et al.* (*Clinical Cancer Research*, **7**:2537-2544, August 2001) discusses results where antisense oligonucleotide against protein kinase alpha type I (PKAI) inhibit expression *in vitro* and show antitumor activity *in vivo*. In Tortora the authors combine PKAI antisense compounds with bcl-2 antisense compounds and demonstrate *in vitro* inhibition. Significantly, Tortora also demonstrates anti-tumor activity *in vivo* characterized by reduced tumor volume and increased survival, which was assumed to be due to the inhibition of PKAI and bcl-2. *Id.* In Olson *et al.* (*Clinical Cancer Research*, **7**:3598-3605, November 2001), inhibition of human angiogenin expression is described *in vitro* and *in vivo*. Applicants attach hereto copies of the above-identified references along with other references that demonstrate a correlation between *in vitro* and *in vivo* data. These articles and others available in the art demonstrate that a person of ordinary skill in the art would accept that *in vitro* inhibition of a specific gene's expression ***does*** correlate with *in vivo* inhibition.

In addition, Applicants respectfully remind the Office that the absence of working examples "should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement," and "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970))." (M.P.E.P § 2164.02) Applicants further point out that a determination whether *in vivo* data is sufficient for a drug approval by the Food and Drug Administration is ***not*** the same as a determination whether a correlation exists between *in vitro* and *in vivo* data for patentability purposes. (See, M.P.E.P.

2164.05, "considerations made by the FDA for approving clinical trials are ***different*** from those made by the PTO in determining whether a claim is enabled.") (citations omitted, emphasis added).

Thus, when taken as a whole, the state of the art, at the time of the application's filing, including the references cited by the Office, does ***not*** support the Office's allegation that the field of antisense is unpredictable and that there is no correlation between *in vitro* and *in vivo* results. Therefore, the overall state of the art in the field of antisense does not teach that antisense technology *in vivo* is unpredictable. One of ordinary skill in the art would not agree with the Office's unsupported assertion that *in vitro* data does ***not*** correlate with *in vivo* data. Indeed, the Office has not provided any concrete evidence that the claimed invention is not enabled. Thus, the specification enables the pending claims of the present application.

The Office also cites several references in an attempt to demonstrate that undue experimentation would be required to make and use the present invention *in vivo*. Applicants again assert that the Office has selectively read the cited references without considering other teachings in the references that refute the Office's position.

The Office appears to take the position that because some experimentation ***may*** be required to optimize conditions for inhibiting caspase 7 expression, therefore the experimentation would be undue and the rejected claims lack enablement. This is an incorrect application of the law. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (M.P.E.P. § 2164.06). The present application provides a more than a ***reasonable amount*** of guidance with respect to the direction in which the experimentation should proceed. The present specification outlines the types of compounds that can be used and methods used to inhibit caspase 7 expression in cells and tissues. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *In re Wands*, 8 U.S.P.Q.2d at 1404. The types of experiments that the Office alleges would be required are routinely performed in the art.

According to the Office, Agrawal states:

> [o]ligonucleotides must be taken up by cells in order to be effective... several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency.

(Office Action, page 5). Applicants respectfully assert, however, that the Office has failed to proffer evidence that uptake of oligonucleotides will ***not*** occur. Instead, the Office has cited a reference that acknowledges that "efficient uptake occurs. . .". Applicants again remind the Office that 100% uptake is not required in the rejected claims. Further, as discussed above, the Braasch reference reports the uptake of oligonucleotides to various tissues when admininstered intravenously and even, in some instances, orally.

The Office also alleges that "The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and/or tissues harboring caspase 7 expression such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo*, and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with caspase 7 expression *in vivo*." (Office Action, page 7). The Office, however, appears to have confused the requirements for a drug approval by the Food and Drug Administration and patentability. The Office is reminded that whether the *in vivo* data is sufficient for a drug approval by the Food and Drug Administration is not the same as whether a correlation exists between *in vitro* and *in vivo* data to those of skill in the art for patentability purposes. (See, M.P.E.P. 2164.05, "considerations made by the FDA for approving clinical trials are ***different*** from those made by the PTO in determining whether a claim is enabled", citations omitted, emphasis added).

In addition, the present claims do not require that "all harmful expression is inhibited" or "that healthy expression is permitted appropriately *in vivo*." *Id.* The present invention claims "A method of inhibiting the expression of caspase 7 in cells or

tissues comprising contacting said cells or tissues with the compound of claim 1 so that expression of caspase 7 is inhibited." (See, claim 15). The present invention also relates to "A method of treating an animal having a disease or condition associated with caspase 7 comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claim 1 so that expression of caspase 7 is inhibited." (See, claim 16). Neither claim 15 nor claim 16 requires that "all harmful expression is inhibited." Claims 15 and 16 only recite that expression of caspase 7 is inhibited. Whether the inhibition of caspase 7 is 100% or 1% is simply not relevant to enablement.

Further, it is routine for a person of ordinary skill in the art to identify a disease that is associated with caspase 7 expression *in vivo*. Genetic tests are routinely preformed to determine the genetic basis of a disease. Expression analysis is also routinely performed to determine if a protein or gene is associated with selected diseases. A determination of whether formulations are immunogenic is also routinely performed by the art-skilled.

The present application describes numerous examples of compounds that inhibit the expression of caspase 7. As discussed above, there is a significant correlation between *in vitro* and *in vivo* data. Therefore, the Office has failed to identify any experiments that are not routine in the art.

Applicants respectfully remind the Office that when an applicant submits evidence traversing a rejection, the examiner ***must*** reconsider the patentability of the claimed invention based on consideration of the ***entire record*** with due consideration to the persuasiveness of any arguments. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Applicants respectfully request that the Office reconsider the pending reejction under 35 U.S.C. § 112, first paragraph in view of the the cited references ***in their entirety*** as well as the newly submitted references.

Thus, the Examiner has not established a *prima facie* case of nonenablement. One having ordinary skill in the art would be able to make and use the claimed invention using the application as a guide. Therefore, the claims are enabled by the application. Applicants cite numerous references that support enablement. Based on the evidence as a whole, the claims are enabled -- one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation using the application as a

guide. The field of antisense is not unpredictable. One of ordinary skill in the art would believe that *in vitro* data correlates with *in vivo* data. No undue experimentation is required to practice the pending claims. Thus, the pending claims of the present application are enabled. Accordingly, Applicants respectfully request that the rejection of claims 15-20 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 102(e) and 103

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(e) and 103(a) as allegedly being anticipated by and/or obvious over Chenchik *et al.*, U.S. Patent No. 5,994,076 (hereinafter, the "Chenchik reference"). Applicants respectfully request reconsideration in view of amended claim 1.

Applicants have amended claim 1 to recite that the compound specifically hybridizes with the 5' untranslated region, 5' cap region, intron:exon junction, or translation termination codon region of a nucleic acid molecule encoding human caspase 7 (SEQ ID NO:3), thus rendering the rejection moot. support for this amendment can be found at, for example, pages 6-8 of the specification. The two primers of the Chenchik reference, SEQ ID NOS: 1226 and 1322, hybridize to the 3' untranslated region and coding region, respectively. The Chenchik reference does not teach any of the compounds recited in amended claim 1, which hybridize to different regions. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Notwithstanding the foregoing, in regard to the rejection under 35 U.S.C. § 103(a), what the Office Action appears to assert is that because the two primers of the Chenchik reference (SEQ ID NOs: 1226 and 1322) share 100% sequence identity with residues 1812-1838 and 859-886 of Applicants' specification, respectively, the primers would also inherently inhibit caspase 7 expression. Alternately, the Office appears to suggest that such inhibition would have been obvious. Applicants respectfully submit that this analysis is insufficient to establish a *prima facie* case of obviousness in view of the compounds recited in amended claim 1. Indeed, the Office Action fails to carry out any obviousness analysis, let alone provide any motivation to modify the primers of the Chenchik reference in such a manner so as to arrive at the different compounds recited in

amended claim 1. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

The Bowen Reference

Claims 1 and 2 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bowen *et al.* (Cell Death Diff. 1999, **6**:394-401, hereinafter the "Bowen reference"). Applicants respectfully request reconsideration and withdrawal of the rejection because the Bowen reference fails to teach the claimed subject matter.

The Office Action asserts only that the Bowen reference teaches "an antisense compound that binds with and inhibits the expression of caspase 7." The Office Action does not particularly point out where the Bowen reference makes such a teaching. Upon reviewing the Bowen reference, it appears that the Examiner is referring to the sequence 5'-TCATCTGCCATCCCACAAGG-3', which is reported on page 400 of the Bowen reference. The Bowen reference further asserts that such sequence is a caspase 7 antisense sequence. A portion of the sequence (*e.g.*, TCATCTGCCATC – the first 12 bases of the 20-mer) ***may*** hybridize to a region of SEQ ID NO:3 including the translation initiation codon (*i.e.*, bases 43-54). Applicants were unable to locate any additional portion of SEQ ID NO:3 to which the Bowen antisense compound ***may*** hybridize. The Bowen reference, thus, does not teach any of the compounds recited in amended claim 1, which hybridize to different regions of caspase 7. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Bowen in view of Baracchini

Claims 1-10 and 12-15 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of the Bowen reference in view of Baracchini *et al* (U.S. Patent No. 5,801,154, hereinafter the "Baracchini reference"). Applicants respectfully request reconsideration in view of amended claim 1.

Claim 1 has been amended to recite particular regions of a nucleic acid molecule encoding human caspase 7 to which the recited compounds hybridize. As stated above, the Bowen reference neither teaches nor suggests any of the compounds recited in amended claim 1, which hybridize to different regions.

The Office Action asserts that the Baracchini reference reports modifications of antisense compounds. The reports of these modifications, however, does not cure the deficiencies of the Bowen reference. Indeed, the combination of the Bowen and Baracchini reference would not result in a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human caspase 7 (SEQ ID NO:3), wherein the compound specifically hybridizes with the 5' untranslated region, 5' cap region, intron:exon junction, or translation termination codon region and inhibits the expression of human caspase 7 (SEQ ID NO:3). Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Applicants believe the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Attachments:
Smith *et al.* (*Clinical Cancer Research*, **7**:400-406, February 2001)
Dwyer *et al.* (*Clinical Cancer Research*, **5**: 3977-3982, December 1999)
Miyake *et al.*, (*Clinical Cancer Research*, **6**:1655-1663, May 2000)
Wang *et al.*, (*Clinical Cancer Research*, **7**:3613-3624, November 2001)
Berg *et al.*, (*The Journal of Pharmacology and Experimental Therapeutics*, **298**:477-484, 2001)
Tortora *et al.* (*Clinical Cancer Research*, **7**:2537-2544, August 2001)
Olson *et al.* (*Clinical Cancer Research*, **7**:3598-3605, November 2001)